6. (amended) A functional site descriptor according to claim 5 wherein at least one member of the set of geometric constraints is an atomic position specified by a set of three dimensional coordinates, wherein the atomic position can vary within a preselected [RMSD] root mean square deviation.

7. (amended) A functional site descriptor according to claim 6 wherein the atomic position varies within an [RMSD] root mean square deviation of less than about 3 Å.

REMARKS

Status of the Claims

Groups I, II and III elected

Applicants thank the Examiner for accepting Applicants' traversal arguments regarding Groups I, II and III. Accordingly, the claims of Group I (claims 1 to 19), Group II (claims 20 to 22) and Group IV (claims 43 to 52) were examined.

Claims amended, canceled and added

Claims 1 to 52 as filed are pending (claims 23 to 42 were withdrawn from consideration). In the instant amendment, claims 6 and 7 were amended.

Outstanding Rejections

Claims 1 to 22 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1, 3 to 10, 12, 15 to 22 and 43 to 50 stand rejected under 35 U.S.C. §102(b). Claims 1 to 22 and 43 to 52 stand rejected under 35 U.S.C. §103(a). Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims. Reconsideration of the rejections and objections is respectfully requested.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Claims 6 and 7 are amended to replace the acronym "RMSD" with the art-recognized term "root mean square deviation," which is defined at specification page 22, line 15. Also amended is the specification to correct typographical errors on pages 3 and 19. Attached to this paper Applicants have provided a substitute page 119, as requested in Paper No. 9.

None of the foregoing amendments adds new matter or requires a new search. In any event, Applicants expressly reserve the right to pursue subject matter no longer or not yet claimed in this application in one or more applications that claim priority to it.

Telephonic interviews with Examiner

Applicants thank the Examiner for his helpful comments regarding submission of this CPA amendment and response to prior Office Action on the merits.

Sequence Rules under 37 CFR §§1.821 through 1.825

Applicants' compliance to the Sequence Rules under 37 CFR §§1.821 through 1.825, including a sequence listing in electronic and paper forms, is being submitted under a separate cover to Box Sequence.

Non-Art Related Remarks

With regard to the objection to web sites in the specification, as noted in paragraph 3, page 3, of the Office Action, Applicants note that MPEP 608.01 concerns hyperlinks, not mere citations of a world wide web address. The allegedly objectionable citations are not bounded by "< >", and are thus not hyperlinks or other forms of browser-executable code. Accordingly, this objection may be withdrawn.

Furthermore, the objection to claims 6 and 7, as noted in paragraph 5, page 3, of the Office Action, is now moot in view of the amendments above, and may thus be withdrawn.

Issues under 35 U.S.C. §112, first paragraph

Claims 1 to 22 stand rejected under 35 U.S.C. §112, first paragraph, as being non-enabled because the specification allegedly does not describe "how one can use and apply the method of claims 1 to 22 without a computer." Paper No. 9 at page 4.

Applicants respectfully aver that the specification does, in fact, teach those of ordinary skill in the art how to make and use claimed invention without undue experimentation, as shown below.

As an initial matter, none of claims 1 to 22 are directed to "methods". Instead, they are directed to functional site descriptors (FSDs) (claims 1 to 19) and libraries of FSDs (claims 1 to 22). Various embodiments of Applicants' invention utilize computer-implemented

FSDs. For example, FSDs and libraries of FSDs need not be computer-implemented, as explained in the specification at page 25, lines 20 to 26. As those in the art will appreciate, it is also possible, e.g., to represent FSDs as tactile models. Such models may then be used to examine an actual scale model of a protein, for example, to determine if the spatial arrangement of the atoms defining the FSD also exists in the protein. In short, any useful representation of an FSD of the invention (computer-implemented or otherwise, whether now known or later developed) is taught by the specification, as those in the art will appreciate. The specification both contemplates and enables embodiments of claims 1 to 22 that may be implemented without a computer. Accordingly, because the specification enables embodiments of claims 1-22 that may be implemented without a computer, the instant rejection should be withdrawn.

Issues under 35 U.S.C. §102(b)

Holm, et al.

Claims 1, 3-10, 12, 15-22, and 43-50 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Holm, *et al.* (1997) PROTEINS: Structure, Function and Genetics 28:72-82 (hereinafter "Holm").

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. Applicants respectfully traverse because the cited reference does not teach each and every element of Applicants' claims.

Holm purports to report global structural conservation patterns in amidohydrolases related to urease. Notably, nowhere does it identify a subset of geometric constraints that represent only an active or other functional site of these proteins. Rather, the authors specifically reported that "[R]esidue-by-residue optimal alignment and superimposition of three-dimensional structures reveals a common structural core consisting of an ellipsoidal $(\beta\alpha)_8$ barrel with a conserved metal binding site at the C-terminal end of strands β_1, β_5, β_6, and β_8" (Holm, page 72, right-hand column).

In contrast, Applicants' claimed FSDs comprise a set of geometric constraints for one or more atoms in each of two or more amino acid residues comprising a functional site of a

protein other than a divalent metal ion binding site.[1] Using such an FSD, as opposed to a global structural fold of a protein, one is able to determine if a protein probed with the FSD contains the corresponding site, and hence the corresponding activity. Holm does not provide such information or FSDs. Accordingly, the claimed invention is not anticipated by Holm.

Regarding the Patent Office's comments for claims 20 to 22 (page 7, lines 4 to 9), these claims concern libraries of functional site descriptors, not libraries of protein structures.

In conclusion, because Holm fails to teach or suggest, explicitly or inherently, each and every element of Applicants' claims, it is not anticipatory. Accordingly, the 35 U.S.C. §102 rejection should be withdrawn.

Issues under 35 U.S.C. §103(a)

Wallace, et al.

Claims 1 to 22 and 43 to 52 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Wallace, *et al.* (1996) Protein Science 5:1001-1013 (hereinafter "Wallace").

Applicants respectfully traverse the Examiner's analysis of the claimed invention in consideration of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). *See* Paper No. 9 at page 8.

In particular, Wallace purportedly concerns automated methods for deriving "functional templates" for the catalytic residues of certain proteins, specifically, the catalytic triad of serine proteases and lipases. The reported template was based on the positions of one or more catalytically functional side chain atoms of the amino acid residues of the purported active site. Residues were reportedly selected to be interacting if at least one interatomic contact [between side chains atoms of "interacting" residues] was less than the sum of the van der Waals radii of the contacting atoms plus 1 Å (see Wallace at page 1004). Initially, the RMS distance of all Ser and Asp side chain atoms were calculated relative to a seed triad. *Id.* This purportedly led to the observation that two side chain oxygen atoms, one from each residue, appeared to be involved in the catalytic function of the catalytic triad. *Id.* The three dimensional positions of these two functional oxygen atoms were then reportedly used to make the first template

[1] See, e.g., claim 1, page 144, line 14 to 22, of the specification.

mentioned by Wallace. A second template, made of all non-hydrogen side chain atoms of the Ser and Asp residues (including the functional oxygen atoms), was then said to have been generated.

In contrast, Applicants' claimed FSDs incorporate one or more non-catalytic backbone atoms. Nothing in Wallace suggests that a functional site descriptor can be accurately represented by non-catalytic backbone atoms. Moreover, to build an FSD according to Applicants' invention, it is not necessary to begin with all non-hydrogen side chain atoms of the residues involved in particular biological activity in order to identify the functionally important side chain atoms.

As discussed above, Wallace would not have motivated one of ordinary skill in the art to make a geometric representation of a protein functional site incorporating one or more non-catalytic backbone atoms. Indeed, Wallace's reliance on inclusion of catalytically functional atoms teaches away from Applicants' invention. Furthermore, Wallace does not suggest that an FSD that incorporates one or more non-functional backbone atoms, *e.g.*, an α-carbon, amide nitrogen, carbonyl oxygen, and β-carbon, but not catalytically functional side chain atoms from at least two amino acid residues implicated in the particular biological activity, could reasonably be expected to allow the successful identification of a protein functional site. Applicants respectfully submit that the invention of claims 1 to 22 and 43 to 52 is not obvious over Wallace within the meaning of 35 U.S.C. §103 and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing remarks, it is believed that the Examiner should withdraw the rejection of the pending claims under 35 U.S.C. §112, first paragraph, 35 U.S.C. §102(b) and 35 U.S.C. §103(a). Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Nov. 30, 2000

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